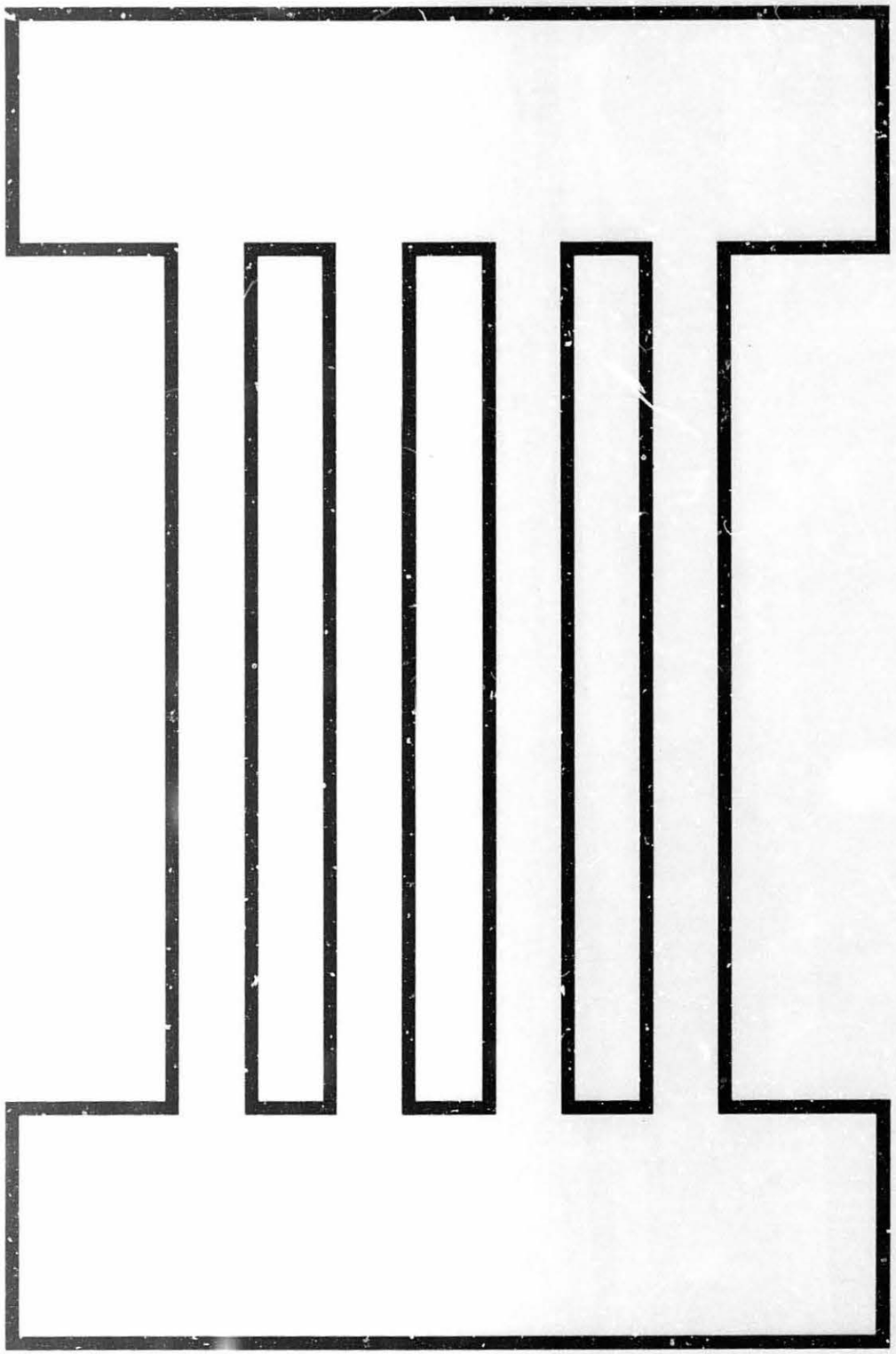

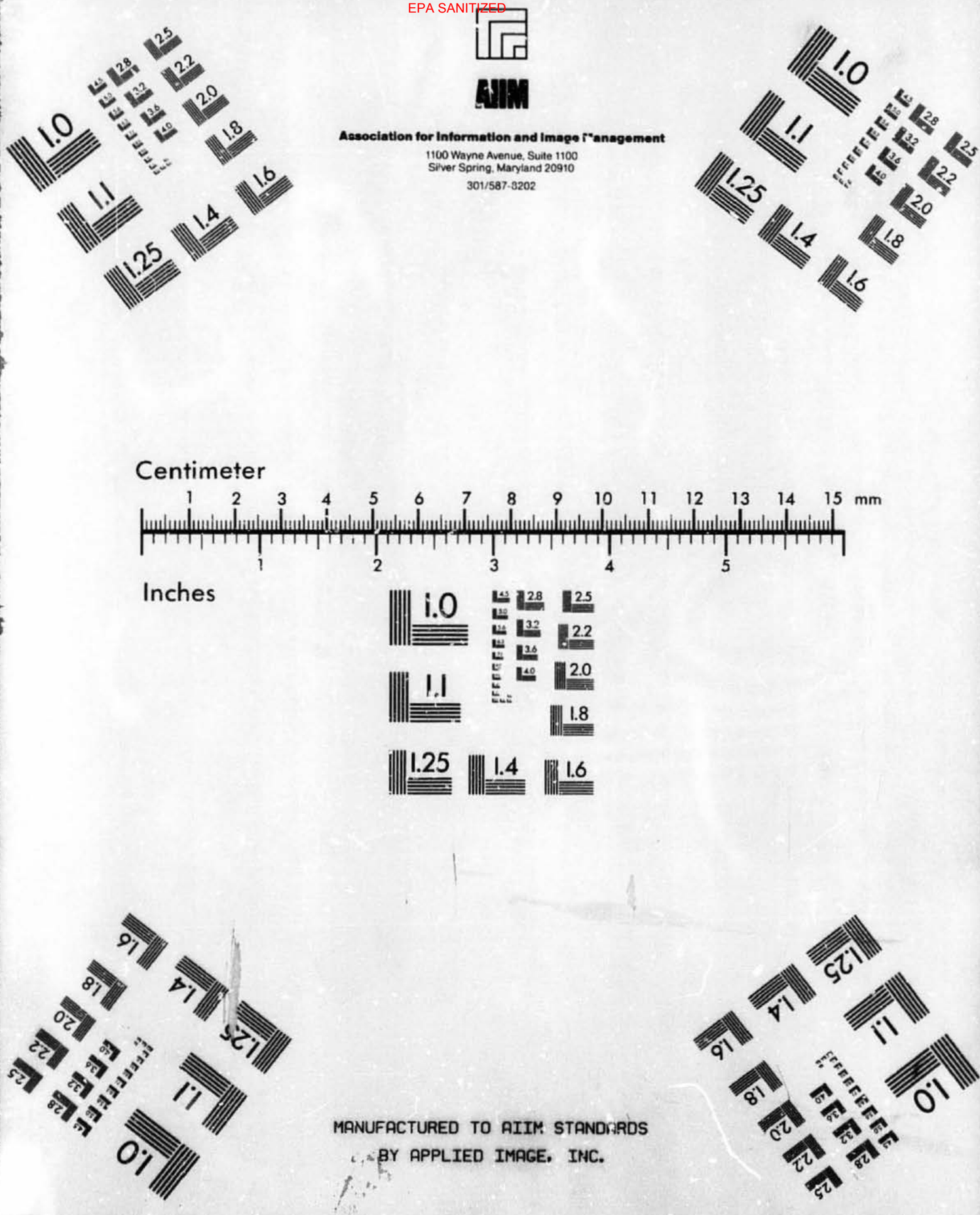

This file contains 9 pages

ADDENDUM TITLE PAGE

PMN FILE NUMBER 89-632

ADDENDUM LETTER B

DATE 8-22-90

THE BEST COPIES AVAILABLE WERE USED FOR THIS FILE

The documents included on this addendum fiche were received after the original PMN file was filmed.

Addenda are indexed and filmed several times a year. They are filed behind the original file fiche.

Please check with the [redacted] Center staff if the document you are looking for is not included in the PMN file or any of its addenda.

Addendum prepared by: CJG

Document Processing Center (DPC)
Confidential Business Information Center (CBIC)
information Control Section (ICS)
Chemical Information Branch (CIB)
Information Managerment Division (IMD)
Office of Toxic Subtances (OTS)

[redacted]

[redacted]

[redacted]

April 12, 1990

Recd 4/24/90

Ms. Cathy Fehrenbacher
U.S. Environmental Protection Agency
Mail Code TS 779
401 M Street SW
Washington, DC 20460

RE: PMN P89-632

Dear Ms. Fehrenbacher:

Thank you for taking the time to consider my question regarding the protective clothing recommendations for our product (P89-632). As we discussed, it appears that TYVEK would be a suitable material for protective clothing to use against dermal exposure to this product. This was based on information taken from the TYVEK bulletin (greater than 99% exclusion of particles 0.5 μm and above) and on EPA's assessment of risk as indicated in the consent order for P89-632. In the consent order it was stated that absorption via the dermal route was expected to be poor. Based upon this information you concurred that TYVEK would be a suitable material to protect workers against exposure to this product.

Thank you again for providing assistance in this matter. If you have any comments please let me know.

Sincerely,

[redacted]

[redacted]

[redacted]

[redacted]

50-908000997

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

[redacted]

APR 30 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

[redacted]

Re: P89-632

Dear [redacted]

The Environmental Protection Agency (EPA) has reviewed the submitted protocols for a 14-day range finding study and 90-day subchronic oral feeding study on the chemical substance described in premanufacture notice (PMN) P-89-632. EPA's comments and recommendations on the proposed protocols are designed to avoid potential problems so that the results of the studies will be scientifically valid test data. Under no circumstance does approval of the test protocol mean pre-acceptance of test results. The following are EPA's comments on the study:

The protocols do not contain any provisions for immunotoxicity or testicular toxicity testing, as specified in the consent order. The following tests should be added to the protocols to meet the requirements:

o Preservation, gross pathological and histopathological examination of the sternum with bone marrow, thymus, spleen, a representative lumph node, testes and epididymides.

o Determination of the cellularity of the bone marrow, thymus and spleen.

o Determination of the absolute and relative weights of the thymus, spleen and testes.

o Leukocyte differential count.

Two additional changes in the protocols should be made:

o Staging of the sperm should be conducted in all male animals in the 90-day study.

o The 90-day study should state that the lungs will be weighed and preserved by perfusion with a fixative.

EPA-OTS

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50-90900:530

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CONCURRENCES							
SYMBOL	TS794	TS-794	TS-794				
SURNAME	Birnbaum	Stoglebauer	Allison				
DATE	4/26/90	4/26/90	4/27/90				

EPA Form 1320-1 (12-70)

000002

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If you have any questions or comments, please contact Rona Birnbaum, the Program Manager assigned to this PMN, at (202) 245-4142.

Sincerely,

Rose Allison
Section Chief
New Chemicals Branch

[redacted]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

[redacted]

[redacted]

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

NOV 29 1989

Dear [redacted]

Enclosed are two originals of pages 22 and 24 of the Consent Order for P-89-632. They contain the corrections we discussed on the telephone. Page 22 was corrected to read "completely [redacted] in the polymer [redacted] replacing "[redacted]." The typo on page 24 was corrected to read "the effect of this Distribution section" replacing "the effect of this Testing section."

Please replace the previous pages with the new ones in both original copies of the Consent Order. Thank you for your cooperation. Feel free to call me with any further questions you may have.

Sincerely,

Rona Birnbaum

Rona Birnbaum, Program Manager
New Chemicals Branch

000004

[redacted]

[redacted] - continued:

c. Histopathological Evaluations:

Slides of tissues listed in Appendix B (under Microscopic Examination) will be prepared and examined microscopically for all animals in the control and high-dose groups sacrificed after 3 months of treatment. Slides of lungs, liver, kidneys and any target organs/tissues identified by evaluations of high-dose animals will be examined for low- and mid-dose animals. Target organs will be designated by the Study Director, Pathologist and/or Sponsor based on experimental findings; authorization will be obtained from the Sponsor prior to performing examinations. Note: Any abnormalities not noted during gross postmortem examinations which are seen during histological processing will be recorded. Examinations of all gross lesions and target tissues in the low- and mid-dose groups will be performed at additional cost. Authorization of the sponsor will be obtained prior to the evaluation of low- and mid-dose target tissues. Tissues from recovery animals will not be evaluated unless authorized by the sponsor (additional cost).

All tissue sections, including those of the testes, epididymides and ovaries, will be examined for the presence of microscopically visible morphologic abnormalities. When applicable, these will be graded on a scale of 1-5. This grading system reflects a subjective assessment of the degree to which a specific section of tissue is involved; in event of multiple sections, the grading is based upon a composite assessment. The various severity grades used are generally defined as the approximate percentage of the tissue section involved; these are as follows:

1- (minimal)	up to 2%
2- (slight)	from 2% - 10%
3- (moderate)	from 10% - 30%
4- (marked)	from 30% - 70%
5- (extreme)	over 70%

This grading system is further expanded to indicate that the finding is focal, multifocal or difuse in distribution. For all paired organs, the unilateral or bilateral occurrence of findings is also noted.

Regarding the testes, microscopic evaluation will include an assessment of the relationships between spermatogonia, spermatocytes, spermatids and spermatozoa seen in cross sections of the seminiferous tubules. The progression of these cellular associations define the cycle of spermatogenesis. Alterations in these cell of the normal spermatogenic cycle. In addition, the testes will be examined for the presence of degenerative changes--e.g., vacuolization of the germinal epithelium, multinucleated giant cells, a decrease in the thickness of the germinal epithelium, a preponderance of Sertoli cells, sperm stasis, inflammatory changes, mineralization and fibrosis. The variable degrees of arrest of the spermatogenic cycle and the degenerative changes will be graded as previously stated.

XI. POSTMORTEM - continued:

C. Histopathological Evaluations:

Regarding the epididymides, special attention will be given to the relative numbers of spermatozoa and the presence or absence of degenerated seminal product (cellular debris) within the tubular lumens. Findings in the epididymides should reflect those seen in the testes. Morphologic abnormalities seen in the epididymides will be graded as previously stated.

In the ovaries, special attention will be given to the presence of oocytes, follicles and corpora lutea regarding their number and size in order to ascertain the progression of their normal development. Abnormalities in their development as well as any degenerative changes, atretric follicles or other findings will be noted and graded as previously described.

The procedures described here for the postmortem examination of tissues and organs, including those of the reproductive system, have been used successfully to identify morphologic abnormalities which occur sporadically as well as those induced by a wide variety of test articles.

M. Stains:

Hematoxylin and eosin. Other appropriate stains may be employed at the discretion of the study pathologist (additional cost) following consultation with the sponsor.

XII. RECORDS TO BE MAINTAINED; PRESERVATION OF TEST RECORDS AND SPECIMENS:

All data documenting experimental details and study procedures and observations will be recorded and maintained as raw data.

At the completion of the study, all reports, raw data, preserved specimens and retained samples will be maintained in the Bio/dynamics, Inc. Archives for a period of one year after submission of the signed final report.

Approximately one year after the issuance of the final report the sponsor will be contacted in order to determine the final disposition of these materials. The sponsor is responsible for all cost associated with the storage of these materials beyond one year from the issuance of the final report and for any costs associated with the shipment of these materials to the sponsor or to any other facility designated by the sponsor.

XIII. STATISTICAL EVALUATIONS:

The following items will be analyzed statistically in the final report:

mean body weight values and body weight changes (from pretest)
mean food consumption values (presented as grams of food/kg of body weight/day)
mean clinical laboratory values
mean terminal organ weights, organ/body weight ratios and organ/brain weight ratios

000006

United States Environmental Protection Agency

EPA

[redacted]

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Document Control Officer	Date

Document Description	Document Control Number
P87-632 Correspondence from Sub	52-90800997

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Washington, DC 20460

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Document Description	**Document Control Number**
P89-632 Protocol Review Letter	50-90D02539

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Dixon	Rall	31493	4/27/90

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COMPUTER SCIENCES CORPORATION
APPLIED TECHNOLOGY DIVISION

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